Essais randomisés en clusters

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Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

UNIVERSITÉ FRANÇOIS - RABELAIS TOURS FACULTÉ DE MÉDECINE

Essais randomisés

- Etude expérimentale visant à évaluer l'efficacité d'un nouveau traitement ou d'une nouvelle intervention
- En le comparant au traitement habituel ou à la prise en charge de référence
- Randomisation :Tirage au sort permettant une répartition au hasard, aléatoire, des patients dans les deux groupes

BMJ

RESEARCH

Cryotherapy versus salicylic acid for the treatment of plantar warts (verrucae): a randomised controlled trial

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ABSTRACT

Objective To compare the clinical effectiveness of cryotherapy versus salicylic acid for the treatment of plantar warts.

Design A multicentre, open, two arm randomised controlled trial.

Setting University podiatry school clinics, NHS podiatry clinics, and primary care in England, Scotland, and Ireland.

Participants 240 patients aged 12 years and over, with a plantar wart that in the opinion of the healthcare professional was suitable for treatment with both cryotherapy and salicylic acid.

Interventions Cryotherapy with liquid nitrogen delivered by a healthcare professional, up to four treatments two to three weeks apart. Patient self treatment with 50% salicylic acid (Verrugon) daily up to a maximum of eight weeks.

Main outcome measures Complete clearance of all plantar warts at 12 weeks. Secondary outcomes were (a) number of plantar warts at 12 weeks (incident rate ratio 1.08 (0.81 to 1.43), P=0.62).

Conclusions Salicylic acid and the cryotherapy were equally effective for clearance of plantar warts.

Trial registration Current Controlled Trials ISRCTN18994246, National Research Register N0484189151.

INTRODUCTION

Verrucae (or plantar warts) are extremely common, being experienced by most people at some time during their lives. Studies that have examined the prevalence of warts or verrucae have produced a wide range of estimates—from 0.84% in the US,[1] 3.3% to 4.7% in the UK,[2,3] and up to 24% in 16–18 year olds in Australia.[4] Although most plantar warts will spontaneously disappear without treatment,[5,6] many patients seek treatment for a variety of reasons, including discomfort or because they are prevented from doing sports and other activities of daily living. Almost two million peo-

Essais randomisés en clusters

- Essai randomisé en grappes
- « *A cluster randomization trial is one in which intact social units, or clusters of individuals, rather than individuals themselves, are randomized to different intervention groups* »
- Cluster randomization trial (CRT)

Allan Donner, *Design and analysis of cluster randomization trials in health research* (London: Arnold, 2000).

Essais randomisés en clusters

- Utilisation croissante depuis 30 ans

- Interventions de santé publique
- Programmes d'éducation pour la santé dans les écoles
- Interventions visant à modifier le comportement des professionnels de santé

Exemple d’unités de randomisation

- Hôpitaux, services médicaux, médecins
- Maisons de retraite
- Zones géographiques (villages, régions …)
- Ecoles
- Familles
- …

Identification and Referral to Improve Safety (IRIS) of women experiencing domestic violence with a primary care training and support programme: a cluster randomised controlled trial

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See Comment page 1760

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Summary

Background Most clinicians have no training about domestic violence, fail to identify patients experiencing abuse, and are uncertain about management after disclosure. We tested the effectiveness of a programme of training and support in primary health-care practices to increase identification of women experiencing domestic violence and their referral to specialist advocacy services.

Methods In this cluster randomised controlled trial, we selected general practices in two urban primary care trusts, Hackney (London) and Bristol, UK. Practices in which investigators from this trial were employed or those who did not use electronic records were excluded. Practices were stratified by proportion of female doctors, postgraduate training status, number of patients registered, and percentage of practice population on low incomes. Within every primary care trust area, we randomised practices with a computer-minimisation programme with a random component to intervention or control groups. The intervention programme included practice-based training sessions, a prompt within the medical record to ask about abuse, and a referral pathway to a named domestic violence advocate, who also delivered the training and further consultancy. The primary outcome was recorded referral of patients to domestic violence advocacy services. The prespecified secondary outcome was recorded identification of domestic violence in the electronic medical records of the general practice. Poisson regression analyses accounting for clustering were done for all practices receiving the intervention. Practice staff and research associates were not masked and patients were not aware they were part of a study. This study is registered at Current Controlled Trials, ISRCTN74012786.

Findings We randomised 51 (61%) of 84 eligible general practices in Hackney and Bristol. Of these, 24 received a training and support programme, 24 did not receive the programme, and three dropped out before the trial started. 1 year after the second training session, the 24 intervention practices recorded 223 referrals of patients to advocacy and the 24 control practices recorded 12 referrals (adjusted intervention rate ratio 22·1 [95% CI 11·5–42·4]). Intervention practices recorded 641 disclosures of domestic violence and control practices recorded 236 (adjusted intervention rate ratio 3·1 [95% CI 2·2–4·3). No adverse events were recorded.

Interpretation A training and support programme targeted at primary care clinicians and administrative staff improved referral to specialist domestic violence agencies and recorded identification of women experiencing domestic violence. Our findings reduce the uncertainty about the benefit of training and support interventions in primary care settings for domestic violence and show that screening of women patients for domestic violence is not a necessary condition for improved identification and referral to advocacy services.

Funding Health Foundation.

L'intervention testée s'applique à l'échelon « cluster » et non individuel.

- Unité de randomisation : cabinets de médecine générale (K=51)
- Intervention : Sessions d'entraînement multidisciplinaires, mail, entretiens téléphoniques, « pop-up » dans le dossier…
  - But: Améliorer l'identification, le soutien et la prise en charge des femmes victimes de violences domestiques
- Contrôle : « Comme d'habitude »
- Critère de jugement :
  - Nb d'orientations de patientes vers des services spécialisés
  - Nb d'identification de violences domestiques dans les dossiers médicaux informatisés

ARTIST (osteoarthritis intervention standardized) study of standardised consultation versus usual care for patients with osteoarthritis of the knee in primary care in France: pragmatic randomised controlled trial

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ABSTRACT

Objective To evaluate the impact of standardised consultations on patients with osteoarthritis of the knee.

Design Open pragmatic cluster randomised controlled trial.

Setting Primary care in France.

Participants 198 primary care rheumatologists, each of whom had to include two consecutive patients who met the American College of Rheumatology criteria for osteoarthritis of the knee.

Interventions Standardised consultation was provided during three goal oriented visits (education on osteoarthritis and treatment management; information on physical exercises; information on weight loss) or usual care.

Main outcome measures Change in body weight and in time spent on physical exercises (Baecke index) at four months.

Results 336 patients were included (154 allocated to standardised consultation and 182 to usual care). Nine patients were excluded because of lack of baseline data

INTRODUCTION

Osteoarthritis is a major source of morbidity, disability, and loss of function in the general population.[1] In an ageing population, osteoarthritis of the knee is likely to be of increasing concern. The guidelines for treatment of osteoarthritis of the knee from the National Institute for Health and Clinical Excellence, the American College of Rheumatology, and the European League Against Rheumatism recommend non-drug treatments,[2-5] including education of patients, social support, physical exercises, and weight loss.[6] However, despite these recommendations, such non-drug treatments are not systematically offered to patients in clinical practice. For example, less than half of obese patients with osteoarthritis of the knee have been advised by a healthcare professional to lose weight.[7-9]

Managing a chronic disease such as osteoarthritis requires a modification of patients' behaviour; patients need to be educated about the disease and to understand the purpose of the treatment proposed. However, providing such complex interventions is time consuming and difficult to do in the context of short

L'intervention testée s'applique à l'échelon « cluster » et non individuel.

- Unité de randomisation: Rhumatologues (K=198)
- Intervention:
  - Consultations standardisées pour les patient ayant une arthrose du genou
    - Une consultation : Arthrose et traitement
    - Une consultation : Exercice physique
    - Une consultation : Perte de poids
- Contrôle : Usual care
- Critère de jugement : Evolution du poids, durée d'exercice physique à 4 mois

L’intervention testée s’applique à l’échelon « cluster » et non individuel.

- Médecin ne peut pas prendre en charge différemment 2 de ses patients
- Deux médecins travaillant dans le même cabinet doivent avoir la même attitude

Effectiveness of a Randomized School-Based Intervention Involving Families and Teachers to Prevent Excessive Weight Gain among Adolescents in Brazil

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Abstract

Objective: To evaluate the effectiveness of a school-based intervention involving the families and teachers that aimed to promote healthy eating habits in adolescents; the ultimate aim of the intervention was to reduce the increase in body mass index (BMI) of the students.

Design: Paired cluster randomized school-based trial conducted with a sample of fifth graders.

Setting: Twenty classes were randomly assigned into either an intervention group or a control group.

Participants: From a total of 574 eligible students, 559 students participated in the study (intervention: 10 classes with 277 participants; control: 10 classes with 282 participants). The mean age of students was 11 years.

Intervention: Students attended 9 nutritional education sessions during the 2010 academic year. Parents/guardians and teachers received information on the same subjects.

Main Outcome Measurement: Changes in BMI and percentage of body fat.

Results: Intention-to-treat analysis showed that changes in BMI were not significantly different between the 2 groups ($\beta = 0.003$; $p = 0.75$). There was a major reduction in the consumption of sugar-sweetened beverages and cookies in the intervention group; students in this group also consumed more fruits.

Conclusion: Encouraging the adoption of healthy eating habits promoted important changes in the adolescent diet, but this did not lead to a reduction in BMI gain. Strategies based exclusively on the quality of diet may not reduce weight gain among adolescents.

Trial Registration: Clinicaltrials.gov NCT01046474.

Eviter les interactions entre les sujets des 2 bras de randomisation

- Unité de randomisation : Classes (K=20)
- Intervention: 9 sessions d'éducation nutritionnelle
- Critère de jugement:
  - Evolution du BMI et du pourcentage de masse grasse à un an
- Eviter une mesure biaisée de l'effet de l'intervention si on avait randomisé les élèves

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Ivermectin versus Malathion Lotion for Difficult-to-Treat Head Lice

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ABSTRACT

BACKGROUND

Head-lice infestation is prevalent worldwide, especially in children 3 to 11 years old. Topical insecticides (i.e., pyrethroids and malathion) used as a lotion, applied twice at an interval of 7 to 11 days, are typically used for treatment. Resistance of lice to insecticides, particularly pyrethroids, results in treatment failure. The efficacy of alternative agents is controversial.

METHODS

We conducted a multicenter, cluster-randomized, double-blind, double-dummy, controlled trial comparing oral ivermectin (at a dose of 400 μg per kilogram of body weight) with 0.5% malathion lotion, each given on days 1 and 8, for patients with live lice not eradicated by topical insecticide used 2 to 6 weeks before enrollment. The cluster was defined as the household. Infestation was confirmed and monitored by means of fine-toothed combing. Patients were at least 2 years of age and weighed at least 15 kg; all were treated at the study sites. The primary end point was the absence of head lice on day 15.

RESULTS

A total of 812 patients from 376 households were randomly assigned to receive either ivermectin or malathion. In the intention-to-treat population, 95.2% of patients

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This article (10.1056/NEJMoa0905471) was updated on April 28, 2010, at NEJM.org.

Eviter la contamination

- Unité de randomisation : famille/foyer (K=376)
- Traitement des poux résistants à un premier ttt local
- Intervention : Ivermectine orale
- Contrôle : Malathion en lotion
- Double aveugle
- Critère de jugement : Présence de poux à J15
- Eviter qu'un sujet reçoive un traitement qui échoue et contamine un autre membre de sa famille ayant reçu l'autre traitement

Pourquoi randomiser des clusters ?

- Contraintes logistiques / administratives
  - Ex : Intervention = personnel supplémentaire
- Meilleure compliance
  - Ex : Essai régime alimentaire
- Meilleure coopération des investigateurs
- Raisons éthiques
  - Ex : médecin veut faire bénéficier tous ses patients d'un nouveau programme de dépistage

Unité de randomisation / Unité d'analyse

- Souvent randomisation de clusters mais inférences au niveau individuel.
- Unité de randomisation ≠ Unité d'analyse
- Problème : pas d'indépendance des individus au sein d'un cluster, présence d'une corrélation intracluster

Conséquences de la corrélation intracluster

- Conséquence statistique dans un CRT : présence d'une corrélation intracluster (intraclasse)

  Les réponses de deux sujets d'un même cluster sont plus ressemblantes que les réponses de deux sujets de clusters différents.

Conséquences méthodologiques

- Prise en compte dans le calcul d'effectif
  - Augmentation du nombre de sujets nécessaires
  - Utilisation des formules classiques du calcul de nombre de sujets nécessaires avec un facteur d'inflation

Conséquences méthodologiques

- Prise en compte dans l'analyse statistique :
  - Méthodes statistiques adaptées
  - Risque de conclusion erronée : inflation de l'erreur alpha

Conséquences méthodologiques

- Randomisation antérieure à l'inclusion
  - On randomise des clusters, puis chaque responsable de cluster inclut des sujets
    - Ex: ARTIST
  - Risque de biais de sélection
    - Niveau de recrutement
    - Profil des sujets inclus
- Absence d'aveugle
  - Interventions à l'étude bien souvent non médicamenteuses et difficile à planifier en aveugle

Aspects éthiques

- A quel niveau recueillir le consentement ?
  - Au niveau du cluster (the « guardian » or « gatekeeper »)
  - Au niveau individuel
- Le recueil du consentement individuel est-il possible ?
  - Risque de contamination (ex : programme éducationnel)
  - Aspects logistiques (ex : cluster=région)
- Les individus ont-ils la possibilité de se soustraire à l'intervention ? (Ex : traitement de l'air par insecticide)
  - Légitimité du « guardian » à consentir pour le cluster

Hutton JL. *Stat Med* 2001;20(3):473-88.

Conclusion

- Les essais randomisés en cluster sont des essais complexes tant au niveau de leur planification que de leur analyse.
- Mise en œuvre doit être justifiée et rigoureuse

~~Merci de votre attention~~

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Sources de la corrélation intracluster

- Individus choisissent souvent le cluster auquel ils appartiennent
  - Caractéristiques individuelles et choix du médecin
- Covariables importantes au niveau cluster influencent les sujets d'un même cluster de la même façon
  - Famille et même environnement, facteurs génétiques
  - Municipalités et lois anti-tabac
- Interaction fréquente des individus au sein d'un cluster -> réponse similaire
  - Ex ASSIST
- Cas des maladies infectieuses : propagation plus rapidement au sein des familles ou des services hospitaliers